Risk Factors for Acute Wheezing in Infants and Children: Viruses, Passive Smoke, and IgE Antibodies to Inhalant Allergens

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Funding Support:

This work was supported by National Institutes of Health Grants AI-24261 and AI-20565. Additional support was provided by the University of Virginia Children's Medical Center.

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KEYWORDS: asthma, bronchiolitis, inhalant allergy, viral respiratory tract infection, environmental tobacco smoke

ABBREVIATIONS:

- RAST, radioallergosorbent test
- RSV, respiratory syncytial virus
- GM, geometric mean
- CI, confidence interval

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ABSTRACT

Objective: To examine the prevalence of viral infection, passive smoke exposure, and IgE antibody to inhaled allergens in infants and children treated for acute wheezing.

Design: Case-control study of actively wheezing children who were compared to children without respiratory tract symptoms.

Setting: University of Virginia Pediatric Emergency Room.

Patients: Convenience sample of 99 wheezing patients (2 months to 16 years) and 57 control patients (6 months to 16 years).

Measurements and Results: Serum IgE antibody to inhalant allergens, measured by RAST, was uncommon in wheezing and control patients under age 2. After age 2, the percentage of RAST positive patients increased markedly and was significantly higher in wheezing patients than controls after age four (72%, n=54, and 30%, n=40, respectively, $p<0.001$). Total IgE levels and nasal eosinophilia were strongly correlated with a positive RAST after age 2. Viral pathogens, predominantly RSV, were identified in nasal washes from 70% (n=20) of wheezing patients under age 2 compared to 20% of controls (n=10), $p<0.05$. After age 2, viruses, particularly rhinovirus, were isolated in washes from 31% (n=70) of wheezing patients, 64% of whom were also RAST positive. Cotinine, a nicotine metabolite, was elevated (≥10ng/ml) in saliva from a large percentage of smoke exposed wheezing patients under age 2 (74%, n=19) compared to those over age 2 (14%, n=51), $p<0.001$. Odds rations for wheezing were significant for virus (8.2, CI=1.3-5.0), and cotinine (4.7, CI=1.0-21.3) in children under 2, and IgE antibody by RAST (4.5, CI=2.0-10.2), virus (3.7, CI=1.3-10.6) and the combination of IgE antibody and virus (10.8, CI=1.9-59.0) were significant risk factors over age 2.

Conclusion: Wheezing children under age 2 had a high rate of viral infection and a low rate of IgE antibody to inhalant allergens. When these children were exposed to

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passive smoke, salivary cotinine levels were elevated suggesting heavy exposure. After age 2, sensitization to inhaled allergens became increasingly important and viruses remained a significant risk factor for wheezing. These data support recommendations to reduce tobacco smoke exposure at home, especially for young patients, and to consider sensitization to inhaled allergens and allergen avoidance in wheezing children at an early age, particularly after age 2.

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INTRODUCTION

Over the past decade, mortality due to asthma in children has increased (1). Hospitalization rates for wheezing prior to age 17 have risen by 4.5% per year with children under age four contributing disproportionately to this statistic (2). These changes have occurred despite our expanding knowledge about the pathophysiology of asthma and emphasis on the usage of anti-inflammatory medications (3). Although some patients experience persistent wheezing, many children have acute wheezing episodes followed by periods of remission. Contributing to the increasing morbidity associated with asthma, environmental exposures to air pollution (4), the overuse of inhaled beta-agonists (5), inadequate anti-inflammatory medications (6), and poor access to health care for medically indigent patients have been cited as causes (7). In addition, exposure to inhaled allergens, viral infections and passive tobacco smoke exposure have been correlated with airway hyper-reactivity in a number of studies (8-10).

In infants, wheezing is often diagnosed as bronchiolitis, and a strong association between viral respiratory tract infections (particularly RSV) and wheezing episodes has been shown (11). Although the prevalence of sensitization (i.e. IgE antibody) to inhalant allergens is not clear among infants who wheeze, prospective studies of infants born to allergic families found that IgE antibody to these allergens was not commonly detected before age two (12, 13). In older children, viral pathogens continue to be a risk factor for wheezing (9). In addition, sensitization to inhaled allergens, particularly to dust mite allergen, has been demonstrated in up to 60-80% of school-aged children with asthma (14-15). Passive tobacco smoke exposure has been shown to increase airway hyperresponsiveness in young infants (16), is related to persistent wheezing in grade school asthmatics (17), and is a more common exposure among children from lower socio-economic backgrounds (18).

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The purpose of the present study was to examine the relationship of sensitization to inhaled allergens, viral infection, and passive smoke exposure in a non-selected population of infants and children treated for wheezing in a pediatric emergency room. An additional objective was to determine at what age IgE antibody to inhalant allergens in these children can be demonstrated as a risk factor for wheezing.

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METHODS

Study Population

Study participants included 99 children presenting to the University of Virginia Pediatric Emergency Room from September 1988 through March 1992 with the diagnosis of bronchiolitis or asthma. Entering wheezing patients were from 2 months to 16 years of age, had wheezing documented by auscultation, required treatment with at least a beta-agonist, and had no history suggestive of bronchopulmonary dysplasia. No patient enrolled in the study had taken systemic steroids prior to his/her emergency room visit. Fifty-seven control patients were enrolled in the same setting and were excluded if they had respiratory symptoms at the time of presentation or a previous history of wheezing.

Additional information was obtained from family members by questionnaire and included questions regarding immediate family history (in parents and siblings) for allergic disease, birth history, breast feeding, patient's allergic history and home tobacco smoke exposure. This study was approved by the human investigation committee at the University of Virginia and informed written consent was obtained from parents and/or subjects.

The University of Virginia is a regional medical center for Central Virginia with approximately 400 pediatric emergency room visits for wheezing annually. Most wheezing children under age 2 present to this emergency room from November through March, whereas older asthmatics present more frequently in the spring and fall. In the present study, the majority of patients (94%) were enrolled during the months of September through June. Seventy-eight percent of wheezing children under age two were enrolled from November through February and 74% of the wheezing patients over age 2 were enrolled over a similar time period (October through February). Seventeen percent of all wheezing patients were admitted to the hospital for further management.

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Additional demographic characteristics of the study population are presented in Table 1.

Immunoassays

Serum from patients was obtained by venipuncture and stored at -20°C until analyzed for IgE antibody to inhalant allergens and for total IgE. Allergen specific IgE antibody was measured by quantitative RAST using cyanogen bromide activated filter paper discs coated with extracts from Miles Inc., Hollister-Stier Division, Spokane, WA, as previously described (8). Briefly, the allergen extracts used included dust mite (*D. pteronyssinus* and *D. farinae* tested separately), cat epithelium, short ragweed pollen, rye grass pollen, and mixed cockroach containing allergens from German, American, and Oriental species. Discs coated with extracts were then incubated with patient's serum (diluted 1/4 and 1/16) and IgE antibody bound to allergen was detected using radiolabelled goat anti-human IgE. Using *D.Farinae* coated discs, a reference control curve was established for each assay with serial two-fold dilutions of pooled serum containing 2500 RAST units/ml of IgE antibody to *D.Farinae*. Three negative and three positive control sera were run with each assay. Sera containing ≥40 RAST units/ml to an allergen (equivalent to ~4 ng/ml of allergen specific IgE antibody) were considered positive (8). Total serum IgE was measured using a monoclonal antibody based radioimmunoassay described previously (8).

Virology

For young children (e.g. less than age 5) approximately one ml of normal saline was instilled into each nostril and secretions aspirated using a Tym-Tap disposable aspirator (Xomed Products, Inc., Jacksonville, FL). Approximately two ml of saline were instilled into the nares of older patients as they held their breath, after which they blew their retained secretions into a sterile plastic cup. The secretions were then transferred to

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vials containing one ml of a veal infusion broth (pH 7.4) containing vancomycin (20 μg/ml), gentamicin (50 μg/ml) and amphotericin B (1 μg/ml). For the detection of RSV, cell pellets were processed within 4 hours, and a commercially prepared direct fluorescent antibody assay was used to stain for RSV antigen (Ortho Diagnostic Systems, Inc., Raritan, NJ). Duplicate monolayers of primary rhesus monkey kidney, human embryonic lung fibroblast (WI-38 strain), A-549, and Ohio HeLa cell lines were inoculated with 0.2 ml volumes of sample from each patient to isolate parainfluenza (types 1,2,3, and 4) virus, RSV, rhinovirus, adenovirus, influenza A and B viruses, and enterovirus using standard techniques.

Nasal Smears for Eosinophils

After obtaining nasal washes, a cotton swab was used to transfer excess mucoid secretions from beneath the inferior turbinate of the nose to a glass slide. When dry, secretions were treated with Hansel's stain (Lide Laboratories, Florissant, MD) and each slide was examined under oil immersion by three individuals who recorded the total number of eosinophils present per 100 cells counted on three or more fields. Using mean values recorded by the three examiners, nasal smears containing greater than 10 eosinophils/100 cells counted were regarded as positive and indicative of at least moderate eosinophilia as judged by a scale proposed by Lim (19).

Tobacco Smoke Exposure Measurements

In addition to obtaining information about the number of smokers in the home, saliva samples were collected from each patient. The samples were centrifuged to remove mucin and the supernatants were stored at -20°C. Cotinine, a principal metabolic derivative of nicotine, was measured using an inhibition radioimmunoassay previously described (20). This assay is sensitive for cotinine levels $\geq$1.0 ng/ml. An excellent correlation between serum and salivary cotinine determinations has been reported using

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this assay, and others have reported a close relationship between saliva, serum, and urine measurements in distinguishing active from non-active smokers (21, 22).

Statistical Analysis

To compare wheezing patients and controls, logistic regression models were derived and the presence or absence of wheezing was used as the dependent variable (23). Other variables, such as the presence or absence of virus or IgE antibody by RAST, were used as independent variables. A significant regression coefficient associated with one of the latter variables indicates that the variable is able to discriminate between wheezing patients and controls. Regression coefficients from these models were used to estimate odds ratios and 95% confidence intervals. When samples were small we relied on Fisher's exact test (23). Two sample t-tests were used to compare continuous variables between wheezing patients and controls in the different age groups. All tests of significance were two sided.

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RESULTS

IgE Antibody and Eosinophils

Of the twenty-three patients under age 2 who presented with wheezing, only two (9%) had specific IgE antibody to one or more of the inhalant allergens tested (i.e. were RAST positive) (Figure 1A). Both of these patients were 22 months old and had IgE antibody to dust mite allergen (one also had IgE to rye grass). In this age group, no control patient had IgE antibody to the allergens tested. Only one nasal smear, from one of the 22 month old RAST positive patients, contained greater than 10 eosinophils/100 cells counted (Figure 2). Among 21 wheezing patients between 2 and 4 years of age, sera from 35% were RAST positive compared to 20% from controls (Figure 1A). In this age group, 32% of the wheezing patients, all but one of whom were RAST positive, had positive nasal smears for eosinophils (Figure 2).

Over the age of 4, 72% of the wheezing children were RAST positive compared to 30% of controls, $p < 0.001$ (Figure 1A). Most of the RAST positive patients (86%) had IgE antibody to dust mite allergen (Figure 1B). Nasal smears were positive for eosinophilia in 52% of wheezing patients in this age group, compared to 16% of the controls, $p<0.001$ (Figure 2). Among wheezing patients with a positive nasal smear, 91% were also RAST positive. Among the RAST positive wheezing patients, 64% had a positive smear.

Questionnaire analysis for family history showed a higher prevalence of allergy related symptoms (asthma, rhinitis, and eczema) in immediate family members of wheezing patients, compared to controls older than age two, $p<0.001$ (Table 1). This difference was not apparent prior to age two. Measurements of total serum IgE revealed low levels for both wheezing and control patients under age two (Table 1). Over age two, total IgE levels for wheezing patients differed significantly from controls, $p<0.001$.

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A rise in total serum IgE was evident in wheezing children from 2 to 4 years of age (GM=86 IU/ml; 95% CI, 37 to 196 IU/ml) and, in addition, RAST positive wheezing patients after age two had significantly higher total IgE levels than the RAST negative patients (GM=365 and 67 IU/ml, respectively, $p<0.001$).

Detection of Viruses

Cultures from 70% of nasal washes from wheezing patients under age two were positive for virus (Figure 3). Of these, ten (50%) were positive for RSV, three for rhinovirus, one for influenza B, and one was positive for both RSV and enterovirus. In children over the age of two, 31% of the cultures from washes were positive for virus. Sixteen were positive for rhinovirus, only three for RSV, two for enterovirus, and one for influenza A. Among this virus positive group, 64% (14 of 22 patients) were also found to be RAST positive. However, the percentages of virus positive washes from RAST positive and RAST negative wheezing patients were similar (14/44=32% and 8/24=33%, respectively). In both age groups, significantly fewer washes from control patients were positive for virus (Figure 3).

Smoke Exposure

Seventy-five percent of all wheezing patients and 58% of control patients had one or more smokers present at home as judged by questionnaire. Analysis of cotinine concentrations in saliva revealed high levels in many of the children under the age of two. The geometric mean of cotinine determinations was significantly elevated for wheezing patients compared to controls (9.8 and 4.3 ng/ml, respectively, $p<0.05$); however, fewer control patients were exposed to smoke at home (Fig. 4). After age two, cotinine concentrations in saliva from wheezing and control patients did not differ significantly (GM=3.6 and 3.5 ng/ml, respectively). In previous studies of salivary cotinine, levels ≥10ng/ml have been reported to be indicative of heavy passive smoke

Range?

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exposure (24). Among the smoke exposed patients in this study, cotinine levels ≥10 ng/ml were detected in a significantly larger percentage of wheezing children under age two (74%, n=19) as compared to wheezing children over age two (14%, n=51), p<0.001 (Fig. 4). All wheezing and control patients with cotinine levels ≥10ng/ml (n=27) were noted to be exposed to one or more smokers at home by questionnaire analysis, except one (Fig. 4).

Combined Risk Factors

Sixty-six percent of wheezing patients in the study had evidence for two or more of the risk factors examined compared to 28% of control patients, p<0.001. Under age 2, 67% of wheezing patients had both exposure to tobacco smoke and a positive viral culture. Over age 2, 64% had at least two of the three risk factors. Odds ratios based on logistic regression models were used to examine the significance of positive RAST's, viral cultures, and heavy passive smoke exposure (cotinine ≥10 ng/ml) in wheezing children relative to controls (Table 2). Children less than age two in this study were 8 times more likely to be wheezing if they had a positive viral culture than if they did not. They were also more likely to be wheezing if they had cotinine levels ≥ 10 ng/ml. Among children over age 2, RAST positivity was strongly associated with wheezing, and viral infection remained a significant risk factor. In addition, the combination of IgE antibody by RAST together with a positive viral culture was present in 14 wheezing children over the age of two as compared to none of the controls, p<0.001.

COTININE · RR = 4.7 (1.0 – 21.3) <2a

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(1) AS 1.0 IS INCLUDED, NOT SIGN

RR = 0.6 (0.2 – 2.2)

(1) BENEFICIAL EFFECT? HORMESIS?

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DISCUSSION

This study was designed to investigate the prevalence of IgE ab to inhaled allergens, viral infections, and tobacco smoke exposure in infants and children treated for wheezing in a pediatric emergency room. To detect allergen sensitization, serum IgE antibody was measured by RAST because skin testing actively wheezing patients is contraindicated. In our laboratory RAST has been established for five inhalant allergens to which clinic patients react frequently on skin tests (i.e., 97% of skin test positive children with asthma react to one or more of these allergens). In addition, the selection of these allergens is in keeping with the inhaled allergens used in other population surveys (8, 25).

Among wheezing patients under age two, IgE antibody to inhaled allergens was uncommon. This finding is consistent with prospective studies of infants born to allergic parents in whom sensitization to these allergens, determined by skin tests or RAST, was also infrequent prior to age 2 (12, 13). In one of these studies, a cohort of children was followed periodically until age 11 (26). Results showed that exposure to increased levels of dust mite allergen in early childhood was a significant factor in the subsequent development of asthma suggesting that early allergen avoidance may be important for high risk children. Among high risk children are also those who present with atopic dermatitis during infancy who have been shown to have an increased risk for developing respiratory allergies and asthma (27). These children may also present with bronchiolitis. In our study, none of the young wheezing patients under two had signs or symptoms of atopic dermatitis.

An increased prevalence of IgE antibody to inhalant allergens was evident in

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wheezing patients after age two and a significant association between wheezing and sensitization was observed after age four. In keeping with other studies of asthma in children, most of the RAST positive patients were sensitized to dust mite allergen (14, 15), although in drier climates mite sensitization may be less common and IgE antibody to other allergens may be more prevalent. After age 2, a strong correlation between RAST positivity and total IgE levels was evident in the wheezing children. In addition, the increasing prevalence of IgE antibody to inhalant allergens was paralleled by an increase in nasal eosinophilia observed in wheezing patients after age two. Eosinophils are thought to play an important role in the late phase events of immediate hypersensitivity reactions (28). Their presence on nasal smears is also consistent with a response to allergen exposure as judged by their appearance in nasal secretions from grass allergic individuals during the grass pollen season as well as following intranasal allergen provocation (19, 29).

Altogether, viral infections put children both under and over the age of two at significant risk for wheezing. Although the association between viral respiratory infections and wheezing has been described in other epidemiologic investigations (9, 11, 30), this is the first report to compare specific viruses isolated from younger and older children who were treated for wheezing in an emergency room. Our data from wheezing patients under two years support the importance of RSV as a major respiratory pathogen for wheezing in infants (11, 31). None of the virus infected children less than age two however, had IgE antibody to inhaled allergens. In previous studies, an IgE mediated mechanism for wheezing was proposed for some infants with bronchiolitis based on the detection of IgE antibody specific for RSV antigen in nasopharyngeal secretions (32).

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More recently, increased levels of eosinophil cationic protein were also reported in nasal secretions from RSV infected infants (33). In addition, eosinophils have been described in some nasal smears from a study of infants with bronchiolitis; however, a large proportion of these patients had atopic dermatitis (34). By contrast, nasal eosinophilia was not observed in smears from any of the RSV or other virus infected children under age 2 in our study. After the age of 2, virus was isolated from approximately one-third of the washes from children who presented with wheezing, and rhinovirus was the most prevalent pathogen.

The prevalence of tobacco smoke exposure at home was high for wheezing and control patients. Under the age of two, however, a larger proportion of wheezing patients than controls were exposed to tobacco smoke. Studies of smoking trends in the United States indicate that rates of cigarette smoking are higher among lower socioeconomic groups (35). Consistent with this, the income status of our patients, judged by the proportion of the emergency room bill charged to parents, was lower for the wheezing children under age two than for controls. Similarly, the income status of all smoke exposed patients was lower than for non-exposed patients. WHEEZ = f(SOCIAL STATUS) ? AND MOTHERS SMOKE BEHAVIOR ?

The most striking finding regarding passive smoke exposure was the large proportion of children under age two who had elevated cotinine levels suggesting of heavy smoke exposure. Although cotinine has been detected in breast milk (36), none of the patients under age two were being breast fed at the time of their enrollment. Thus, we speculate that infants and young children, who are likely to be more physically dependent on their parents, may have a higher risk for heavy exposure if their parents smoke. However, a threshold level at which passive smoke exposure becomes clinically

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significant in causing or aggravating airway hyper-responsiveness has not yet been defined. In addition, when combined with other risk factors, the effects of smoke inhalation may be additive such that lower levels of exposure may have adverse consequences even for older children. Nevertheless, a dose response relationship has been supported by studies indicating higher rates of asthma and increased usage of asthma medications in children exposed to mothers who smoke at least 1/2 pack of cigarettes per day (10, 37). A highly significant correlation between asthma severity and the number of cigarettes smoked by the mother, but not the father, has also been reported (38). Preliminary analysis of our data suggests that children under age two, who were exposed to mothers smoking 1/2 pack per day or more, were highly likely to have salivary cotinine levels ≥10 ng/ml. This did not appear to be the case after age two. WHY NOT ? Additional studies of mother's smoking habits together with cotinine determinations in their children may help to further clarify this relationship.

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CONCLUSIONS

Results from this study indicate that children who present to an emergency room for wheezing prior to age two can be characterized as having a high rate of viral respiratory tract infection, particularly RSV, and a low rate of sensitization to inhalant allergens. In addition, eosinophils were not apparent on nasal smears from any of these IgE antibody negative patients. After age two, viral infections, mostly rhinovirus, remained an important risk factor for wheezing. However, IgE antibody to inhalant allergens, especially to dust mite, together with elevated total IgE levels and nasal eosinophilia, became an increasingly significant finding. Passive smoke exposure was common among wheezing children at all ages. However, high salivary cotinine levels suggesting heavy smoke exposure were significantly more common among the children under age 2. CUT-OFF POINT VERY LOW (10ng/ml)

Most wheezing patients in this study presented to the emergency room with two or more of the risk factors examined. The management of wheezing in the emergency room, however, often focuses exclusively on treatment with medications, after which many patients return home to unaltered environments. In an effort to reduce morbidity, our data would encourage efforts to reduce tobacco smoke exposure at home, especially for young patients, and to consider sensitization to inhaled allergens and allergen avoidance (e.g. to dust mite) in wheezing children at an early age, and particularly in those who begin or continue to wheeze after age two.

Acknowledgements:

We are grateful to Kathryn Teng, Joan Redd, and John McGovern for their

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contributions and technical assistance. We would also like to give special thanks to Dr. Robert Abbott, Head, Division of Biostatistics, for his guidance with statistical analysis and to the staff working in the Pediatric Emergency Room at the University of Virginia for their support and assistance in the enrollment of patients.

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LEGENDS FOR FIGURES

Figure 1A:

IgE antibody to inhalant allergens in sera from wheezing patients (black bars) and controls (hatched bars). In each serum, titers of IgE antibody were measured by RAST to dust mite, cat, cockroach, rye grass, and ragweed allergens. Sera containing ≥40 RAST units/ml (approximately equivalent to 4ng of allergen specific IgE ab/ml) to one or more of the allergens tested were defined as being RAST positive.

Figure 1B:

Percentage of sera from all RAST positive wheezing patients (ages 22 months to 16 yrs), n=48, with IgE ab specific for allergens in dust mite, cat, cockroach (CR), rye grass, and ragweed (RW) extracts.

Figure 2:

Eosinophils in nasal secretions. The percentage of nasal smears containing ≥10 eosinophils per 100 cells counted is shown for wheezing patients (black bars) and controls (hatched bars). These smears were regarded as positive and indicative of at least moderate eosinophilia as judged by a scale proposed by Lim (19).

Figure 3:

Viral detection in nasal washes. RSV (black bars) was detected by a direct fluorescent antibody assay and all antigen positive washes were also positive in culture using a WI-38 fibroblast cell line. Hatched bars indicate rhinovirus and open bars indicate other viral isolates. The percentages of cultures positive for virus were significantly greater for wheezing patients compared to controls for children under age two ($p<0.05$) and over age two ($p<0.05$).

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Figure 4:

Salivary cotinine levels. Solid circles indicate children who were exposed to one or more smokers at home by questionnaire analysis. Open circles represent patients who were not exposed. One 14 year old control patient actively smoked (indicated by a star). Cotinine levels at or above 10ng/ml (long hatched line) have been reported to reflect heavy passive smoke exposure (24). Values below 1ng/ml (short dotted line) fell below the limits of the assay.

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Table 1. Patient Characteristics

	CHILDREN < 2		CHILDREN > 2	
	Wheezing Patients (n=23)	Controls (n=11)	Wheezing Patients (n=76)	Controls (n=46)
Mean age(yr)	0.9	1.2	7.1	9.6
Age range(yr)	0.2-1.8	0.5-1.8	2.0-15.4	2.3-16.1
Male(%)	57%	33%	73%	65%
Black(%)	74%	44%	55%	31%
Payment requirement:*				
100%	9%	60%	19%	34%
10-75%	14%	0%	26%	10%
0%	77%	40%	55%	56%
Family history for allergy	61%	73%	81%	36%
Total IgE (IU/ml)‡	15 (9-25)	5 (3-11)	198(135-206)	28(18-41)

* Payment requirement categories reflect the proportion of the emergency room bill charged to the patient's family based on annual family income. Shown above are the percentage of familes required to pay 100%, from 10-75%, or 0% of their child's bill.

‡ Total IgE levels are reported as geometric means followed by 95% confidence intervals in parentheses.

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Table 2. Odds Ratios for Wheezing Among Children with a Positive RAST, Virus Culture, or Elevated Cotinine Level

Risk Factors	Odds Ratios‡ Under age 2	Over age 2
RAST	ǂ	4.5 (2.0-10.2)***
VIRUS	8.2 (1.3-51.0)*	3.7 (1.3-10.6)*
COTININE ≥10ng/ml	4.7 (1.0-21.3)*	0.6 (0.2-2.2)
RAST and VIRUS	ǂ	10.8 (1.9-59.0)***

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

‡ Reported odds ratios are univariate analyses followed in parentheses by 95% confidence intervals.

ǂ Not determined because of insufficient positive patients.

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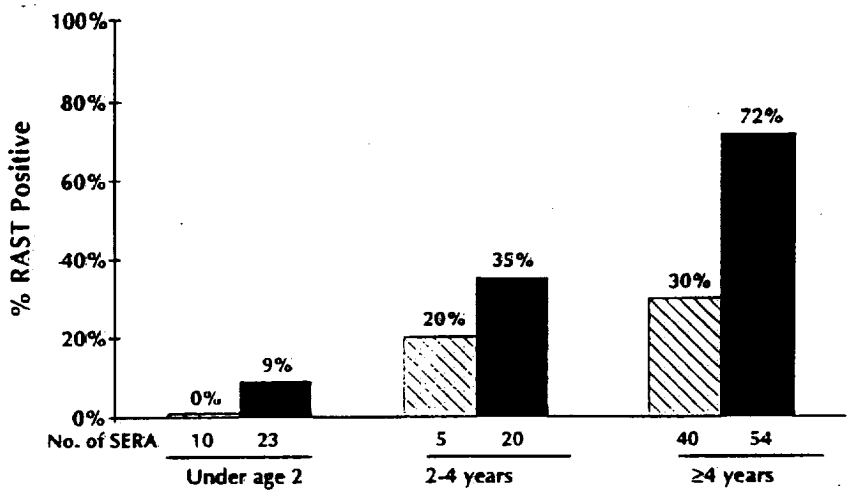

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IgE antibody to inhalant allergens in sera from wheezing patients (black bars) and controls (hatched bars). In each serum, titers of IgE antibody were measured by RAST to dust mite, cat, cockroach, rye grass, and ragweed allergens. Sera containing ≥40 RAST units/ml (approximately equivalent to 4ng of allergen specific IgE ab/ml) to one or more of the allergens tested were defined as being RAST positive.

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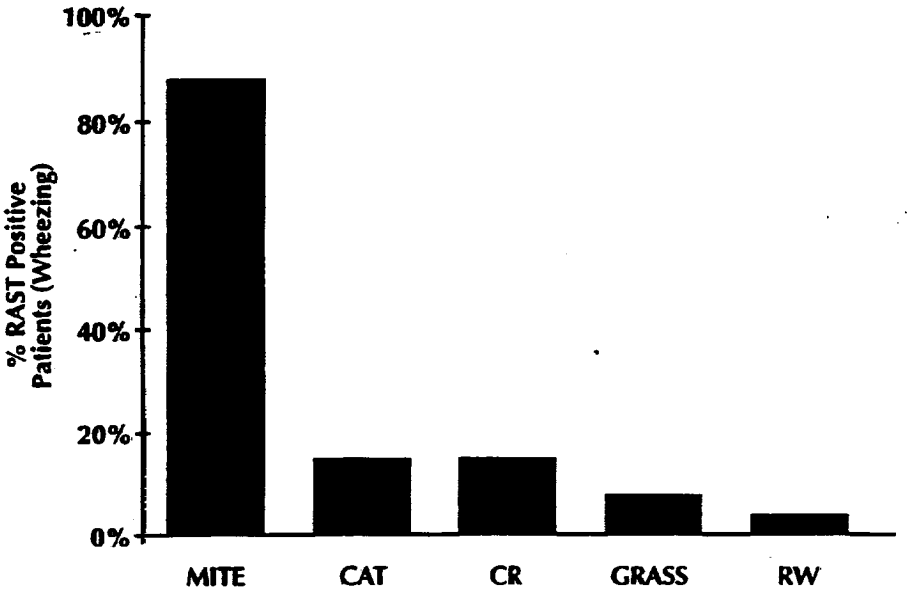

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Percentage of sera from all RAST positive wheezing patients (ages 22 months to 16 yrs) with IgE ab specific for allergens in dust mite, cat, cockroach (CR), rye grass, and ragweed (RW) extracts.

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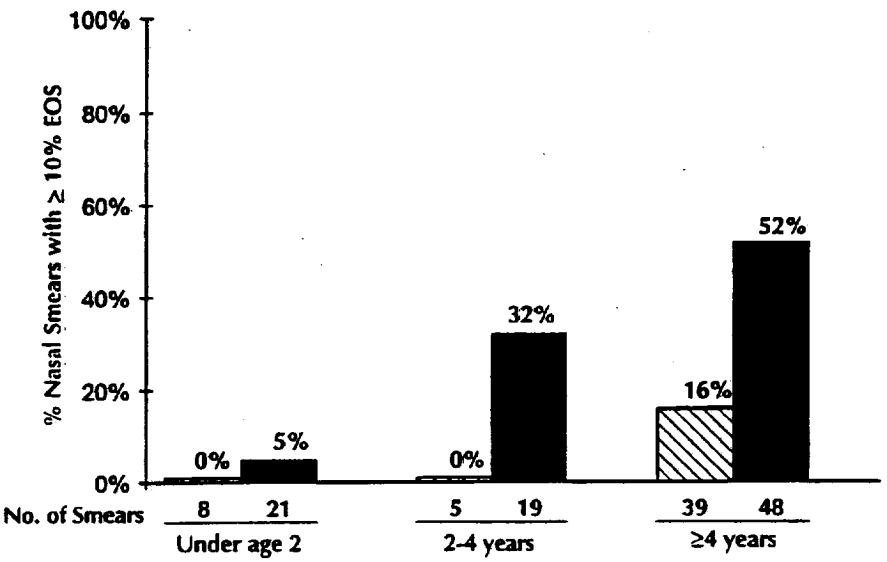

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Eosinophils in nasal secretions. The percentage of nasal smears containing ≥10 eosinophils per 100 cells counted is shown for wheezing patients (black bars) and controls (hatched bars). These smears were regarded as positive and indicative of at least moderate eosinophilia as judged by a scale proposed by Lim (19).

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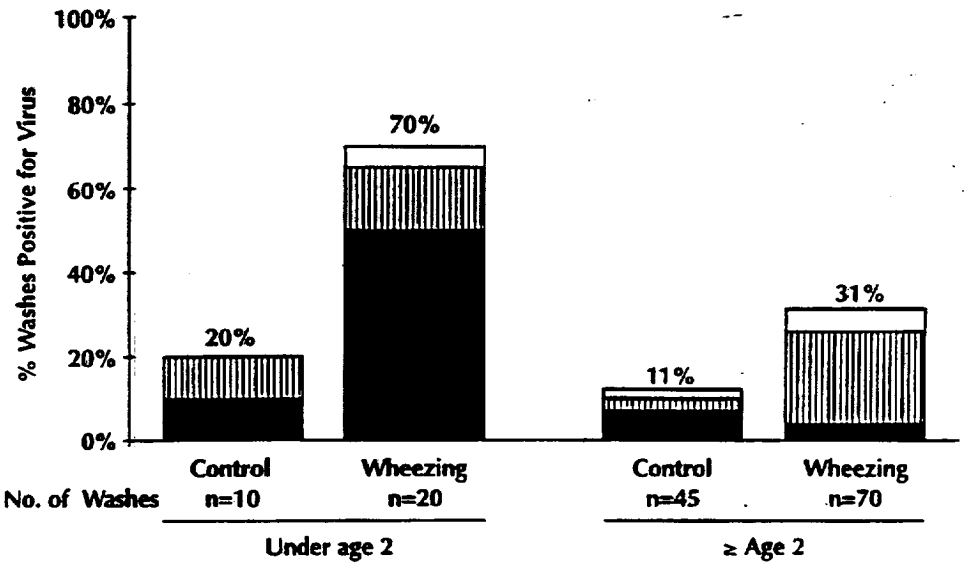

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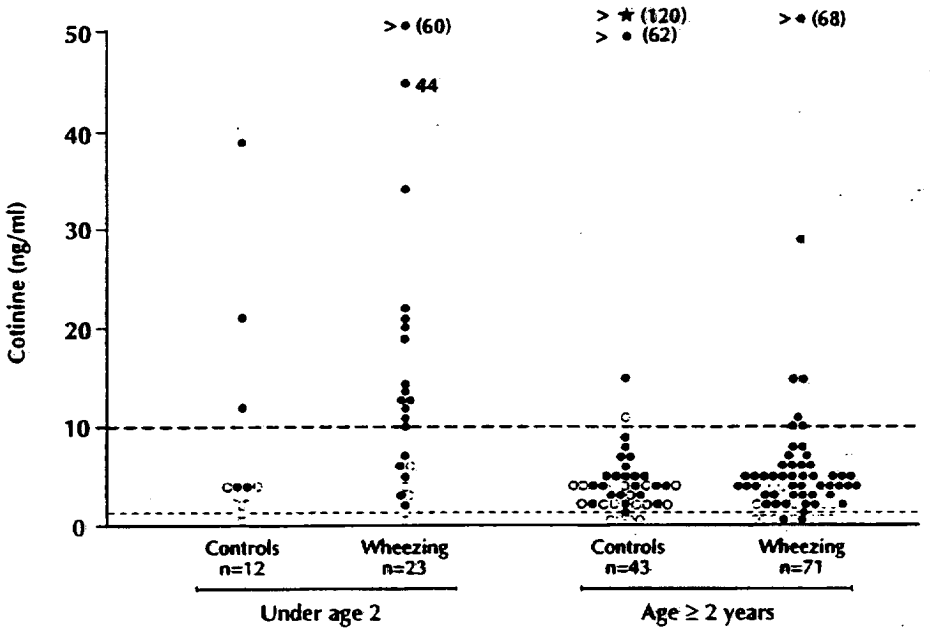

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